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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/077,572 | 10/13/98 | APICELLA | M 875001US2 |

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|---|---|
| DEVI,S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | 11 |

**DATE MAILED:** 04/28/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/077,572 | Applicant(s) Apicella et al. |
|---|---|---|
| | Examiner S. Devi, Ph.D. | Group Art Unit 1641 |

☒ Responsive to communication(s) filed on *Apr 5, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *22-26 and 29* is/~~are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *1-21, 27, and 28* is/~~are~~ [redacted] cancelled.

☒ Claim(s) *22-26 and 29* is/~~are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

**1)** The instant application has been filed as a national stage 371 application of the PCT application, PCT/US96/18984, filed 11/27/1996 with a priority claim to the national application, SN 08/565,943, filed 12/01/95 in the USA. However, the priority status is not provided in the first paragraph of the instant specification.

### Amendment

**2)** Acknowledgment is made of Applicants' preliminary amendment filed 10/13/98 (paper no. 7). With this, Applicants have replaced the original page 69 with the new page 69.

### Information Disclosure Statement

**3)** Acknowledgment is made of Applicants' Information Disclosure Statement filed 11/16/98 (paper no. 8). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 11).

### Election

**4)** Acknowledgment is made of Applicants' election, without traverse, of Invention II, claims 22-26 and 29, filed 05 April 1999 (paper no. 10).

### Claims Status

**5)** Applicants have canceled the non-elected claims 1-21, 27 and 28 through paper no. 10.

Elected claims 22-26 and 29 are pending in this application and are under examination. An Action on the Merits for these claims is issued in the instant Office Action.

### Drawings

**6)** The drawings are objected to under 37 CFR 1.84 because of the reasons set forth by the Draftsperson in the attached Form PTO 948 (paper no. 11). Correction is required.

### Specification/Informalities

**7)** The specification of the instant application is objected to because:

(a) The first paragraph of the instant specification does not disclose the priority status. The priority status of the instant specification needs to be amended to include the prior applications to which priority is claimed.

(b) The recitation "acylxyacyl" hydrolase is not understood on page 12, line 13. Clarification is required.

**Double Patenting**

**8)** The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**9)** Claims 22, 23, 25 and 29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20 and 22 of the copending Application, SN 08/565,943. Although the conflicting claims are not identical, they are not patentably distinct from each other. The method of making in the bacteria of the genera *Haemophilus* or *Neisseria* an endotoxin of substantially reduced toxicity using a *htrB* mutant, an endotoxin of substantially reduced endotoxicity purified from the *htrB* mutant and generation of antibodies to such an endotoxin claimed in claims 19, 20 and 22 of the copending Application are encompassed by the method of making in a Gram negative bacterial pathogen an endotoxin of substantially reduced toxicity using a *htrB* mutant, a mutant endotoxin of substantially reduced endotoxicity purified from the *htrB* mutant and a method of producing endotoxin-specific antisera claimed in claims 22, 23, 25 and 29 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting

claims have not in fact been patented.

**Claims Rejections - 35 U.S.C. §112, First Paragraph**

**10)** Claims 22-26 and 29 are rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure, because the specification does not provide evidence that the biological materials of the claimed invention are (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

It appears that an *htrB* mutant Gram-negative bacterium is required to practice the claimed method of making and using the product, mutant endotoxin, of the instant invention. As required elements, the mutant bacterium must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification. It is unclear if the mutant bacterium is publicly available, or can be reproducibly isolated from nature without undue experimentation. Therefore, suitable deposits for patent purposes is suggested. The specification appears to lack complete deposit information for the *htrB* Gram-negative mutant bacterium that is specifically recited in the instant claims. Without a publicly available deposit of the bacterial mutant, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent on this application and that the deposit will be replaced if viable sample cannot be dispensed by the depository, is required to satisfy the deposit requirements. See 37 CFR 1.801-37 CFR 1.809. Further, the statement should identify the deposited mutant bacterium by its depository accession number, establish that the deposited mutant bacterium is the same as that described in the specification, and establish that the deposited bacterium was in Applicants' possession at the time of filing. *In re Lundak*, 773 F2d 1216, 227 USPQ 90 (Fed. Cir. 1985).

**Claims Rejections - 35 U.S.C. §112, Second Paragraph**

**11)** Claims 23, 24 and 29 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 24 is indefinite in the recitation "comprising conjugation to a carrier protein" because it is unclear what else is encompassed or comprised in this recitation. In order to more clearly define the invention, it is suggested that Applicants replace the recitation with --conjugated to a carrier protein--.

(b) The use of non-idiomatic expression in claim 29, lines 2-4, is confusing. It is suggested that Applicants change this recitation to --for use in diagnostic assays or passive immunization, the method comprising--.

(c) Claim 23 is objected to for reciting "phenol/water extraction". To be consistent with the practice in the art, it is suggested that Applicants change the recitation to –phenol-water extraction–.

**Claims Rejections - 35 U.S.C. §102**

**12)** The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

**13)** Claims 22, 23 and 25 are rejected under 35 U.S.C § 102(a) as being anticipated by Lee *et al.* (*J. Biol. Chem.* 270: 27151-27159, November 1995).

Lee *et al.* teach a method of making in a Gram negative bacterial pathogen, *E. coli*, a mutant endotoxin lacking one or more myristic acid substitutions in the lipid A. Thus, the *htrB* mutants of *E. coli* are taught. The LOS isolated from the *htrB* mutants did not show reactivity with the 6E4 monoclonal antibody which is specific for the wild type LOS. An *htrB* mutant of a non-typable *Haemophilus influenzae* type b is also taught (see abstract; page 27152, left column).

The mutant endotoxin is purified by proteinase K digestion (see the paragraph bridging pages 27152 and 27153). The lipid A of the mutant endotoxin showed a tetraacyl or a pentaacyl species indicative of loss of one or both of the myristic acid substitutions. The *Haemophilus htrB* mutant endotoxin has a 50% reduction in the LOS species containing two phosphoethanolamines (see page 27168, left column).

Claims 22, 23 and 25 are anticipated by Lee *et al.*

**Claims Rejections - 35 U.S.C. §103(a)**

**14)** The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

**15)** Claims 24, 26 and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lee *et al.* (*J. Biol. Chem.* 270: 27151-27159, 1995) as applied to 22 above, and further in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992).

The teachings of Lee *et al.* have been explained above, which do not disclose conjugating the mutant endotoxin to a carrier protein or raising endotoxin-specific antisera as recited in the instant claims for use in diagnostic assays or in passive immunization.

Gupta *et al.* teach conjugating a deacylated endotoxin of a Gram negative bacterial pathogen to a protein carrier to produce an immunogenic conjugate vaccine that can be used to

raise endotoxin-specific antisera by administering it to an animal (see abstract, and pages 3202 and 3203).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Lee's mutant endotoxin lacking one or more myristic acid substitutions in the lipid A to a carrier protein as taught by Gupta *et al.* for a deacylated endotoxin to produce the conjugate of the instant invention and use it in a method of raising endotoxin-specific antisera as taught by Gupta *et al.* for use in passive immunization or in diagnostic assays. One skilled in the art would have had a reasonable expectation of success in producing the conjugate and the method of raising antisera of the instant invention since the *htrB* mutant endotoxin lacking secondary acyl chains is expected to function significantly no differently than the chemically deacylated endotoxin taught by Gupta *et al.* in a conjugate. Absent evidence to the contrary, claims 24, 26 and 29, as a whole, are obvious over the prior art of record.

**16)** Claim 29 is rejected under 35 U.S.C. §103(a) as being unpatentable over Lee *et al.* (*J. Biol. Chem.* 270: 27151-27159, 1995) as applied to 22 above, and further in view of Sprouse *et al.* (US 5,641,492).

The reference of Sprouse *et al.* is applied in this 103 rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Lee *et al.* have been explained above, which do not disclose raising endotoxin-specific antisera as recited in the instant claim for use in diagnostic assays or in passive immunization.

Sprouse *et al.* disclose a method of producing endotoxin-specific antisera for use in passive immunization or for diagnostic purposes by immunizing an individual with a vaccine comprising a mutant Gram negative bacterial pathogen or an endotoxin obtained from the mutant bacterium or a detoxified endotoxin (see columns 3, 4 and 7). The resultant hyperimmune sera provides protection against endotoxin-associated diseases (see column 12, lines 50-55; claim 7 and Figure 3). The hyperimmune serum is also used in a DEAE column (see column 13).

Given the prior art teachings that an *htrB* mutant bacterium produces less toxic endotoxin and that such mutant bacteria or detoxified mutant endotoxin can be used as a vaccine to raise protective antisera for use in passive immunization against Gram negative bacterial infections, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use Lee's bacterial *htrB* mutant or Lee's mutant endotoxin lacking one or more secondary acyl chains to produce endotoxin-specific antisera using Sprouse's method to produce the instant invention with a reasonable expectation of success in using it for passive immunization or for diagnostic purposes.

Claim 29 is obvious over the prior art of record.

**Remarks**

**17)** Claims 22-26 and 29 stand rejected.

**18)** The prior art made of record and not relied upon currently in any rejection is considered pertinent to Applicants' disclosure:

- Karow *et al.* (*J. Bacteriol.* 173: 741-750, 1991) teach isolation and characterization of *E. coli htrB* mutants.
- Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992) teach *E. coli htrB* mutants producing a mutant endotoxin lacking one or more myristic acid and lauric acid (see abstract and pages 7413 and 7416).
- Karow *et al.* (*Mol. Microbiol.* 5: 2285-2292, 1991) teach the sequencing, mutational analysis and transcriptional regulation of the *E. coli htrB* gene.

**19)** Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

**20)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can

normally be reached on Monday to Friday from 8.00 am to 4.00 pm. A message may be left on the Examiner's voice mail service.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 1999

James C. Housel
JAMES C. HOUSEL 4/26/99
SUPERVISORY PATENT EXAMINER